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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,462	12/06/2001	Aillette Mulet Sierra	02451800002	4354

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,462	SIERRA ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *5/30/2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.00

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-13, in the reply filed on 5/26/2005 is acknowledged.

2. Claims 1-18 are pending.

Claims 14-18, drawn to non-elected inventions, are withdrawn from consideration.

Claims 1-13 are examined on the merits.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)

(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Please note that for this application a section entitled "Brief Summary of the Invention" appears to be missing, and the "Brief Description of the Drawings" is incorrectly placed at the end of the specification.

Claim Objections

3. Claims 2-9, 12 and 13 are objected because they are drawn to "*A* vaccine composition according to claim 1". Claims 2-13 are dependent claims and should be drawn to "*The* vaccine composition according to claim 1".

Claim Rejections - 35 USC § 112

4. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is not clear if the phrase "able to produce a specific immune response against said self-TGFα" modifies the claimed vaccine, or the adjuvant. This rejection may be overcome by amending the claim to recite: "wherein the vaccine is able to produce a specific immune response against said self- TGFα".

Claim 7 is indefinite because of the phrase "that contains a chemical conjugated between TGFα and P64k. It is not clear if this phrase means that the claimed composition contains the conjugate or fusion protein of claim 1 and additionally a chemical compound that is used for the purpose of conjugation.

Claims 10 and 11 are indefinite because each is drawn to a vaccine composition "that represents". It is not clear how a composition may "represent" a mix of two vaccine preparations. This rejection may be overcome by amending the claims to recite: "A vaccine composition comprising a mix of two vaccine preparations...".

Claim 10 is further indefinite because the phrase "the chemical conjugated between P64k and TGFα or EGF" lacks antecedent basis.

5. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for vaccines comprising a TGFα molecule sufficiently characterized by physical or chemical structure, such as by SEQ ID NO, does not reasonably provide enablement for vaccines comprising TGFα molecules identified solely as "self-TGFα", "any derived" self-TGFα, "human TGFα", "TGFα" or "hTGFα". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification generally teaches that the purpose of the claimed vaccines is to treat epithelial tumors dependent on TGFα or TGFα/EGF, or in the treatment of any disease associated with TGFα such as psoriasis (page 2, lines 44-46). Therefore, it appears that the function of the claimed vaccines is to cause the production of antibodies that would interfere

with the biological function of TGFα or TGFα/EGF. However, because of the scope of the terms "self-TGFα", "any derived" self-TGFα, "human TGFα", "TGFα" or "hTGFα", as defined in the specification, in comparison with the narrow scope of the working examples provided, it appears that the specification fails to enable the full scope of the claimed vaccines.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The specification defines the scope of the term TGFα as including any fragment derived of TGFα that has the same immunology properties and/or similar effects to the original molecule; the specification further includes original substitutions of amino acids, change of specific amino acids that increase the stability and/or activity, chemical modifications, and other changes to structure (page 2, lines 47-50). Therefore, the claimed vaccines read on compositions comprising protein molecules that include variants of TGFα, such variants including, for example, deletions from, or insertions or substitutions of residues within TGFα. Because of the definition of the terms provided by the specification, the genus of molecules encompassed by the claimed vaccines is large. Furthermore, the study of the relationship between the primary amino acid sequence and protein function is highly unpredictable. Bowie et al (Science, 247: 1306-1310, 1990) teaches that while it is known that many amino acid substitutions are possible in any given protein, the position with the protein sequence where such amino acid substitutions can be

made with a reasonable expectation of maintaining function are limited. Burgess et al (J. Cell Biology, 111: 2129-2138, 1990) teaches that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Lazar et al (Molecular and Cellular Biology, 8: 1247-1252, 1988) teaches that replacement of aspartic acid at position 47 with alanine or asparagines does not affect biological activity while replacement with serine or glutamic acid sharply reduces the biological activity of the protein. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Given that small changes in protein structure may result in large changes to protein structure and function, the claimed vaccines appear to encompass fusion proteins or conjugates that would, if administered to a subject, result in the formation of antibodies that will not bind to a full-length TGFα protein, and therefore, the usefulness of the vaccines, as currently claimed, cannot be determined without further experimentation.

This further experimentation appears to be undue experimentation because of the unpredictability of the protein arts, and because the skilled artisan cannot make and use the broad genus of "self-TGFα", "any derived" self-TGFα, "human TGFα", "TGFα" or "hTGFα" recited in the claims because such a genus encompasses an unlimited and thereby infinite plurality of amino acid substitutions, deletions, additions, or combinations thereof, as compared with the working embodiments. The disclosure does not adequately describe, provide guidance or give examples of the critical amino acid residues that bestow upon "self-TGFα", "any derived" self-

TGFα, "human TGFα", "TGFα" or "hTGFα" the desired characteristics useful for treatment of epithelial cancer or psoriasis by immunotherapy.

6. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the specification fails to provide an adequate description of "derived" self-TGFα. The phrase "any derived" appearing in claim 1, is interpreted to be a reference to derivatives of self-TGFα. Additionally, this rejection is based on the interpretation of the terms "self-TGFα", "human TGFα", "TGFα" or "hTGFα" as each encompassing a genus of molecules that are not adequately described by the specification.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is for purposes of the 'written description' inquiry, "*whatever is now claimed*" (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See Vas-Cath at page 1116.)

The claimed vaccines are drawn to compositions comprising fusion proteins or conjugates of "self-TGFα", "any derived" self-TGFα, "human TGFα", "TGFα" or "hTGFα" with a carrier protein. The specification defines the scope of the term TGFα as including any fragment derived of TGFα that has the same immunology properties and/or similar effects to the

original molecule; the specification further includes original substitutions of amino acids, change of specific amino acids that increase the stability and/or activity, chemical modifications, and other changes to structure (page 2, lines 47-50). Therefore, the claimed vaccines read on compositions comprising protein molecules that include variants of TGFα, such variants including, for example, deletions from, or insertions or substitutions of residues within TGFα. Because of the definition of the terms provided by the specification, the genus of molecules encompassed by the claimed vaccines is large.

The skilled artisan cannot envision the detailed chemical structure of a representative number of molecules encompassed by the terms "self-TGFα", "any derived" self-TGFα, "human TGFα", "TGFα" or "hTGFα", because the specification fails to provide a description of a representative number of molecules within each genus encompassed by each of these terms. This is because the definition appears to include almost any modification to the structure of TGFα, making each genus very large and encompassing structures of wide variation. Furthermore, the specification has failed to provide a nexus between structure and function, with which one of skill in the art may define each genus. This is most true for the genus of "any derived" self-TGFα, which is interpreted to read on "derivatives" of TGFα. A derivative is interpreted broadly as a molecule that may only have in common one atom with the parent molecule.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making or testing it. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the

broad class. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112, is severable from its enablement provision. (See page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1, 3, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Gonzalez (Gonzalez, G. et al., Annals of Oncology, 9: 431-435, 1998).

Claim 1 is drawn to a vaccine composition containing self-TGFα or any derived, coupled with a carrier protein by genetic cloning or by chemical conjugation, wherein the vaccine composition contains an adjuvant. As discussed above, the phrase "any derived" appears to read on derivatives of TGFα. Because "derivatives" are broadly interpreted to include molecules comprising only one atom in common with the parent molecule, a conjugate or fusion of almost any protein with a carrier protein will be encompassed by the claims. Claim 3 adds the limitation that the carrier protein is P64K. Claim 13 adds the limitation that the aduvant is $Al(OH)_3$.

Gonzalez teaches a conjugate between human EGF and either tetanic toxoid (TT) or P64k (P64k Neisseria Meningitidis recombinant protein) (see page 432, 1st column, "Immunogens").

Gonzalez teaches the conjugate comprised within a composition containing aluminum hydroxide. Therefore, Gonzalez teaches a conjugate that is the same as that claimed.

8. Claims 1, 3, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Gonzalez (Gonzalez, G. et al., Vaccine Research, 6(2): 91-100, 1997).

Claim 1 is drawn to a vaccine composition containing self-TGFα or any derived, coupled with a carrier protein by genetic cloning or by chemical conjugation, wherein the vaccine composition contains an adjuvant. As discussed above, the phrase "any derived" appears to read on derivatives of TGFα. Because "derivatives" are broadly interpreted to include molecules comprising only one atom in common with the parent molecule, a conjugate or fusion of almost any protein with a carrier protein will be encompassed by the claims. Claim 3 adds the limitation that the carrier protein is P64K. Claim 12 adds the limitation that the adjuvant is incomplete adjuvant of Freund. Claim 13 adds the limitation that the adjuvant is $Al(OH)_3$.

Gonzalez teaches a fusion protein human EGF and P64k (see page 92-93). Gonzalez teaches the fusion protein comprised within a composition containing aluminum hydroxide or incomplete adjuvant of Freund (page 93). Therefore, Gonzalez teaches a fusion protein that is the same as that claimed.

9. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by either Heimbrook (Heimbrook, D.C. et al., Proc. Natl. Acad. Sci., USA, 87: 4697-4701, 1990) or Kunwar (Kunwar, S. et al., J. Neurosurg., 79: 569-576, 1993) as evidenced by Chaudhary (Chaudhary, V.K. et al. Proc. Natl. Acad. Sci., USA, 84, pp4538-4542, 1987).

Claims 1 and 2 are interpreted broadly to include compositions comprising a fusion protein or conjugate of TGFα and a carrier protein with an intended use as a vaccine.

Heimbrook teaches a fusion protein of human TGFα and PE40 (40kDa segment of the Pseudomonas exotoxin A protein) in combination with phosphate buffered saline (interpreted to be within the scope of an "adjuvant") (see 4698, 1st –2nd column and 4699, 1st-2nd column).

Kunwar also teaches a fusion protein of human TGFα and PE40 (see Chaudhary for evidence that Kunwer's TGFα is human TGFα, page 4538, 2nd column). Kunwer teaches the fusion protein in combination with human serum albumin (interpreted to within the scope of an "adjuvant", see page 570, 2nd column, "Recombinant Proteins"). Kunwer also teaches that the fusion protein construct is immunogenic (see page 574, 2nd column). Therefore, Kunwar teaches a fusion protein that is the same as that claimed. Therefore, either Heimbrook or Kunwar teaches a composition that is the same as that claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 10, 11, 12, 23, and 26 of copending Application No. 10/005,341. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending application 10/005,341 appear to claim compositions that fall within the scope of the vaccine compositions comprising conjugates or fusion proteins of TGFα and a carrier protein.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
August 8, 2005

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER